HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2024 March 27.

Published in final edited form as:

Pediatr Blood Cancer. 2023 March ; 70(3): e30175. doi:10.1002/pbc.30175.

Determinants of delayed childhood cancer care in low- and middle-income countries: A systematic review

Cesia Cotache-Condor[1], **Vinootna Kantety**[1], **Andie Grimm**[2], **Jahsarah Williamson**[1], **Kelsey R Landrum**[3], **Kristin Schroeder**[4,5], **Catherine Staton**[5,6], **Esther Majaliwa**[7], **Shenglan Tang**[5], **Henry E. Rice**[5,8], **Emily R. Smith**[5,6]

[1]Department of Public Health, Baylor University, Waco, Texas, USA

[2]Birmingham's Institute for Cancer Outcomes and Survivorship, University of Alabama, Birmingham, Alabama, USA

[3]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[4]Division of Pediatric Oncology, Department of Pediatrics, Duke University, Durham, North Carolina, USA

[5]Duke Global Health Institute, Duke University, Durham, North Carolina, USA

[6]Division of Emergency Medicine, Department of Surgery, Duke School of Medicine, Duke University, Durham, North Carolina, USA

[7]Division of Pediatric Oncology, Kilimanjaro Christian Medical Centre, Moshi, Tanzania

[8]Division of Pediatric Surgery, Department of Surgery, Duke School of Medicine, Duke University, Durham, North Carolina, USA

Abstract

Early access to care is essential to improve survival rates for childhood cancer. This study evaluates the determinants of delays in childhood cancer care in low- and middle-income countries (LMICs) through a systematic review of the literature. We proposed a novel Three-Delay framework specific to childhood cancer in LMICs by summarizing 43 determinants and 24 risk factors of delayed cancer care from 95 studies. Traditional medicine, household income, lack of

Correspondence Emily R. Smith, Duke School of Medicine, Duke University, 40 Duke Medicine Circle, Durham, NC 27705, USA. emily.smith1@duke.edu.

AUTHOR CONTRIBUTIONS

Cesia Cotache-Condor conceived the study, collected and analyzed the data, produced the visualizations, and drafted the original manuscript. Cesia Cotache-Condor and Vinootna Kantety contributed to all steps in the systematic review section. Andie Grimm and Kelsey R. Landrum contributed to the screening and quality assessment of studies for the systematic review section. Jahsarah Williamson contributed to the screening and data retrieval for the systematic review section. Kristin Schroeder contributed to the research strategy for the systematic review section. Shenglan Tang, Henry E. Rice, and Emily R. Smith contributed to the study design. Emily R. Smith is the guarantor of the systematic review. All authors provided critical input, contributed to the writing, revised and approved the final version of the manuscript before submission.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interestsorpersonalrelationshipsthatcouldhaveappearedtoinfluencethe work reported in this paper.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

transportation, rural population, parental education, and travel distance influenced most domains of our framework. Our novel framework can be used as a policy tool toward improving cancer care and outcomes for children in LMICs.

Keywords

cancer care; global health; health services research; pediatric oncology

1 | INTRODUCTION

Cancer accounts for a large proportion of the global burden of disease in children, ranking as the ninth leading cause of disease for children.[1] The cancer burden in children is disproportionally concentrated in low- and middle-income countries (LMICs), where 85% of cancer cases occur.[2–4] There are wide disparities in survival rates in children with cancer around the world, ranging from 30% in LMICs compared to 80% in high-income countries (HICs).[5–7] The actual extent of disparities is likely underestimated due to data challenges such as the lack of cancer registries and vital registration systems in LMICs.[4,8–10] In this context, the World Health Organization's (WHO) Global Initiative for Childhood Cancer (GICC) has aimed to reach at least a 60% survival rate for children with cancer around the world by 2030.[11]

Many factors contribute to the global differences in cancer outcomes in children, including disparities in access to diagnostics or therapeutics, human resource limitations, financial barriers, lack of supportive care, and more advanced stages of disease when cancer is diagnosed in LMICs.[12] Unlike adult cancers, for which prevention and screening play a significant role, causative genetic and environmental factors of childhood cancers are less understood.[13–15] Early diagnosis and treatment constitute the most powerful approaches to improve survival for childhood cancers.[16] However, children often face long delays in cancer diagnosis, with as low as 30% of children in LMICs receiving timely diagnosis and treatment.[17–19] The Three-Delay Model has been widely used in many areas of global health to evaluate delays in care, with delays described across three domains, including (a) deciding to seek health care; (b) reaching an appropriate health facility; and (c) receiving adequate care when a health facility is reached.[20–23] Understanding how the determinants of delays in care contribute to childhood cancer-related mortality is essential to guide strategic interventions and policy development.

Systematic reviews are critical to guide policy decisions, inform research priorities, and identify gaps in knowledge and are highlighted as a need in oncology research.[24] In addition, rigorous systematic reviews specific to pediatric oncology in LMICs are even further lacking.[25] Our objective was to identify determinants and risk factors of delays in childhood cancer care in LMICs using a systematic review. We used these determinants to propose a Three-Delay framework tailored to childhood cancer across the continuum of care.

2 | METHODS

2.1 | Conceptual framework

All determinants and risk factors of delayed cancer care in this systematic review were organized by adapting several theoretical models (Figure 1).[26] We organized the determinants and factors of delayed care into domains through the Three-Delay Model, a widely used framework in many areas of global health, which summarizes barriers to care associated with seeking, reaching, and receiving health care, depicting the patient's journey from home to the primary health center, all the way up to higher level hospitals.[20–23] The subdomains were organized based on the WHO GICC framework, which longitudinally outlines the childhood cancer continuum of care from detection of symptoms to diagnosis, treatment, and survivorship.[26,27] We intersected the previous domains and subdomains with the Socioecological Model (SEM), a comprehensive framework used in public health interventions. This model is divided into four layers including the following levels: individual (behaviors, perceptions, demographics, etc.), interpersonal and family (socioeconomic factors, social support, etc.), community and organizations (infrastructure, workforce, referral networks, etc.), and policy and environment (health financing schemes, political agenda, etc.).[28] Finally, our framework was aligned with pediatric-specific cancer control plans, including strengthening health systems through an evidence-based, culturally specific implementation framework such as the CureAll program.[26,27]

2.2 | Literature search

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines for the systematic review (Appendix SA).[29] Our detailed protocol, search strategy, and methodology were registered in PROSPERO (CRD42021256128) and were previously published.[30,31] We searched 10 electronic databases and three websites for peer-reviewed studies and grey literature from inception (Appendix SB). Search strings were constructed in compliance with the PICO (Patient, Intervention, Comparison, Outcome) framework,[32] including (a) the Population: children (aged 0–18 years) from LMICs (based on the World Bank classification updated to June 2020),[33] (b) the [I]Exposure: factors contributing to timely childhood cancer care, and (c) the Outcome: delays in childhood cancer care (Appendix SC).

2.3 | Inclusion criteria

Inclusion criteria were determined by compliance with the constructs in the PICO statement. No restrictions regarding language, publication date, outcome effect measure, or quality were applied. Evidence-based studies, including observational studies, qualitative studies, interventions, abstracts, conference papers, reports, and theses and dissertations, were eligible for inclusion. We included grey literature (i.e., WHO Global Index Medicus) to help mitigate the risks of publication bias. Childhood cancer was defined as all-inclusive cancers within this age category according to the International Classification of Childhood Cancer 3rd edition (ICCC-3).[34] Pediatric cancer care was defined as any step across the entire childhood cancer continuum of care. Studies were excluded if they had a sample population over 18 years old, included data from both LMICs and HICs, or examined both adults and children, and did not have a separate analysis for children.

2.4 | Study screening, eligibility, and data extraction

The studies identified through the electronic databases were screened and assessed for eligibility in EPPI reviewer (version 4.12.0.0).[35] Two groups of reviewers (Cesia Cotache-Condor, Andie Grimm, Kelsey R. Landrum, Vinootna Kantety, and Jahsarah Williamson) independently screened in duplicate, with titles, abstracts, and full-text studies assessed against the eligibility criteria. Articles in languages different than English were assessed by a reviewer fluent in that language or translated with Google Translator and verified by a person fluent in that language. The group discussed and resolved by consensus any issues raised during the screening and eligibility processes. If the discrepancies persisted, the final decision was made by another senior coauthor.

Data from all studies meeting the inclusion criteria were extracted by two reviewers (Vinootna Kantety and Jahsarah Williamson). A third reviewer (Cesia Cotache-Condor) independently assessed accuracy of the data extracted on a random subsample of 15% of the studies. Reviewers used a predefined spreadsheet based on the conceptual framework described above to enter information, and any differences between reviewers were resolved by consensus. The retrieved information included title, authors, study design, sample size, age, location, year of publication, outcome, outcome measure effects, exposures (determinants and risk factors of delayed care), study time-frame, measure of delays in receiving care, workforce, infrastructure, out-of-pocket, catastrophic, and impoverishing expenditure. Determinants and risk factors of delayed care were differentiated based on whether they reported effect measures of association (RR = risk ratio, OR = odds ratio, HR = hazard ratio, and aPR = adjusted prevalence ratio). Exposures reporting these measures of association were defined as risk factors. Descriptive statistics were generated using SAS 9·4 (SAS Institute Inc., Cary, NC, USA) and ArcMap 10·3 (ESRI, Redlands, CA). Cancer diagnoses were classified into 13 categories, including general (all cancers), and the 12 categories based on the ICCC-3.[34]

2.5 | Methodological quality appraisal and bias assessment

A total of 61 full-text articles were independently assessed for quality by two groups of reviewers (Vinootna Kantety, Andie Grimm, and Kelsey R. Landrum). A third reviewer (Cesia Cotache-Condor) performed the reconciliation process. Any issues that were raised during the quality assessment process were discussed by the group and resolved by consensus. If discrepancies persisted, the final decision was made by a senior coauthor. An assessment of quantitative studies was performed by using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[36,37] The Critical Appraisal Skills Program (CASP) checklist was used to assess qualitative studies.[38] The Authority, Accuracy, Coverage, Objectivity, Date, Significance (AACODS) checklist was used to evaluate the grey literature.[39] All full-text studies ($n = 61$) were given scores based on their performance in their respective assessment tool. Each tool had a different number of questions (AACODS = 6 sets of questions, CASP = 10 questions, NIH = 14 questions). For all studies, a positive answer (yes) was given the score of “1,” a negative answer was given the score of “−1,” and an unknown answer was given the score of “0.”

For the AACODS tool, the scores were first calculated based on the questions within each set. For each set, if at least 50% of the answers were positive, then the entire set was marked as “yes,” and it was otherwise marked as “no.” Then, we considered every set as one question and proceeded with the methodology explained above. Subscores from each tool item were added to calculate an overall score for each study. Overall scores equal or less than “0” were classified as “low quality.” Overall scores greater than “0” but lower than “5” (qualitative tool) and “7” (quantitative tool) were classified as medium quality. Finally, overall scores equal or greater than “5” (qualitative tool) and “7” (quantitative tool) were classified as high quality.

3 | RESULTS

The systematic review yielded a total of 95 studies that met inclusion criteria (Figure 2). We summarized determinants and risk factors of delayed childhood cancer care from a pooled sample of 39,636 participants among children, caregivers, and healthcare professionals (IHME), the WHO International Agency for Research on Cancer (IARC) (Table 1). Most studies were cross-sectional from hospital settings and evaluated determinants and risk factors of delays to diagnosis. Cancer types varied across studies, including general, site group I (leukemias, myeloproliferative diseases, and myelodysplastic diseases), site group II (lymphomas and reticuloendothelial neoplasms), and site group VIII (malignant bone tumors) representing the most common cancer types and making up to 27%, 9%, and 9% of the total, respectively. Additional details, including population, delays in weeks, time frame, publication, workforce, infrastructure, OPP expenditure, catastrophic expenditure, and impoverishment expenditure, can be found in Appendix SD.

Studies were distributed across 97 LMICs, with the largest number of studies from Africa ($n = 104$) and Nigeria ($n = 11$) at the regional and national levels, respectively (Figure 3). The years with the highest number of publications were 2018 and 2019. The cross-sectional design was most frequently used (59% of reports), while 5%–8% of the studies used a mixed-methods, qualitative, or intervention design. The main outcome reported by the studies was delay in diagnosis with 55% of the total number of studies, followed by treatment initiation (23%), and treatment abandonment (20%). Only 2% of studies discussed delays in receiving palliative care.

From all 95 studies included in this review, we found a total of 43 determinants and 24 risk factors that were associated with delayed childhood cancer care. From a subsample of 61 full-text studies evaluated for quality, half were classified as high quality (50.8%), and half were classified as medium quality (49.2%). No studies were classified as low quality. Further details from the quality appraisal can be found in Appendix SE.

The determinants and risk factors for delays in cancer care were summarized within the Three-Delay framework in three domains (D1: Seeking care, D2: Reaching care, and D3: Receiving care), one subdomain (onset of symptoms) under both “D1: Seeking care” and “D2: Reaching care,” four subdomains under the “D3: Receiving care” (Diagnosis, Referral, Treatment, and Palliative care), and four strata (individual, interpersonal and family, community and organization, and environment and policy) (Figure 4). Traditional

medicine, household income, lack of transportation, rural population, parental education, and travel distance influenced most domains and subdomains. Palliative care was the domain with the most significant lack of data.

When we assessed determinants and risk factors by time point domain along the continuum, seeking care was mainly impacted by individual and family strata, while reaching care was mainly impacted by community and policy strata. Receiving care was the most often reported domain across the continuum. Determinants and risk factors impacting receiving care, specifically treatment, were widely spread between domains. Determinants and risk factors impacting access to diagnosis included lack of cancer knowledge on both individual and the community levels, health system variables, such as multiple referrals and waiting times, and lack of health insurance at the policy level. Referral care was impacted by a household's income, travel distance, rurality, and having a dedicated referral communication contact. The treatment subdomain had a wider range of reported determinants and risk factors of delay compared to the rest of subdomains and domains, with presence across all strata (individual, family, community, and policy). The least studied point in the care continuum was palliative care, with only four predictors, including family resistance, lack of social support, lack of home-based services, and lack of physician palliative care training. Individual and family determinants and risk factors mainly included religious and cancer beliefs, traditional medicine, socioeconomic variables (income, marital status, household duties, parental education), lack of social support, and absence from work. While language and income barriers mainly impacted seeking care, across the community stratum, rurality, travel distance, and lack of transportation impacted both reaching and receiving care, including both referral to a health center and treatment. Barriers in cancer care infrastructure were consistent across the entire domain of receiving care. Across the policy and environmental strata, a country's income level impacted seeking care, neither determinants nor risk factors were found to impact reaching care, and lack of health insurance and a country's income level impacted receiving care.

4 | DISCUSSION

There is an increasing recognition in the global health community of the pressing need to improve cancer care for children, particularly in LMICs that face the highest burden of cancer and the lowest survival rates. The WHO GICC has set a target to improve cancer survival in children to at least 60% by 2030.[11] As reducing delays in cancer diagnosis and initiation of care are among the most effective tools to improve cancer survival for children, a better understanding of how countries are performing in addressing delays in care is essential. Our systematic review suggested that traditional medicine, household income, lack of transportation, rural population, parental education, and travel distance were the leading predictors of delays in childhood cancer care in LMICs. Based on these findings, we propose a Three-Delay Model that can potentially serve as a decision policy tool ready to guide national and regional efforts toward timely care and increased survival among children living with cancer in LMICs.

Cancers are often underdiagnosed or diagnosed at a late stage in LMICs,[4,133] leading to increased mortality rates, higher costs of treatment, abandonment of care, and increased

risks of household impoverishment.[20,134] Improved access to accurate data and data-driven decision tools are essential for government and other policymakers to reduce delays in cancer care for children.[8,135,136] A better understanding of the barriers to timely cancer care is a foundational step toward developing action plans to improve childhood cancer care along the entire continuum of care. The Three-Delay Model offers a comprehensive view that depicts the journey from the patient's home to the healthcare network and the hurdles at each point in time across the continuum of care. Based on examples from other global health fields,[22,23] we adapted this well-known model to understand the trajectory of cancer care and the specific challenges faced by children in LMICs. Unlike previous applications of this framework,[20–23] the Three-Delay Model for childhood cancer care includes three domains (seeking care, reaching care, and receiving care), five subdomains, including onset of symptoms, diagnosis, referral, treatment, and palliative care. These domains and subdomains intersect with the four levels of the SEM, allowing us to dissect and evaluate how specific points of delay relate to endogenous and exogenous variables from a structural point of view.[28]

According to our model, the delay in seeking care starts with the onset of symptoms, and takes place at the family and community level. At this point in time, individual and community factors influence the decision to seek care, and the role of the health system is limited to education, surveillance, and outreach. The delay in reaching care is mainly influenced by factors at the community level and the role of the health system falls on ensuring the patient has a timely and ease of journey to the first healthcare facility, usually a primary health center or a district/first-level hospital. The delay in receiving care is heavily impacted by the health system capacity and takes place from primary health centers all the way up to higher level and specialized hospitals. At this stage, strong referral networks, infrastructure, and workforce capacity ease the patient's journey from a preliminary diagnosis of cancer at the primary health center or district/first-level hospital, to an evidence-based diagnosis, appropriate treatment, and palliative care at higher level and specialized hospitals.

Our study confirmed the existence of multidimensional and multifactorial barriers, preventing timely cancer care for children in LMICs. Therefore, future initiatives need to address the multiple and interacting barriers leading to delays in care, with isolated interventions to address single barriers unlikely to move the needle much to improve outcomes. Comprehensive cancer care packages within the universal health coverage (UHC) schemes should be designed to protect families from financial constraints, develop health system capacity, and enhance necessary support networks for patients, families, and health professionals across the entire continuum of care, with an increased attention to palliative care, the most neglected area across the continuum of care.

The need for capacity-building for childhood cancer systems is frequently inadequately prioritized in national health agendas. The mean health expenditure for cancer care in LMICs is only 6.2% of the global cancer expenditures, despite the high global burden of cancer located in LMICs.[137] Access to diagnostic and treatment services such as adequate number of workforce, medication, and ancillary services such as pathology and laboratory support are all essential to achieve timely and quality cancer care.[138,139] However, our data

suggest that increased financial protection is also a necessary step in the roadmap toward decreasing delays in childhood cancer care in LMICs, to ensure swift seeking, reaching, and receiving care when needed. Caregivers often experience significant out-of-pocket expenses to ensure access to cancer diagnosis and treatment for their children, with financial challenges often leading to delayed care and abandonment of care.[123,126]

Effective scale-up of childhood cancer systems in LMICs requires evidence-based financing streams accord to specific national priorities and sustainable financing mechanisms aligned under the principles of UHC.[140] Innovative financing strategies can include multisectoral public and private partnerships, pooling resources at regional or global levels, or leveraging global health financing facilities.[141,142] These strategies have been successfully implemented in other global health areas, such as malaria, tuberculosis, HIV, and child immunizations, and might be promising for childhood cancer. Specific hospital-level financing systems could include strategies such as giving travel, lodging, and meal vouchers to families from referral hospitals to travel to tertiary hospitals where specialized cancer care is often given, thereby reducing out-of-pocket expenses for the family.

Our study has several limitations. First, limited national-level data were available to measure all barriers of delayed childhood cancer care. This study only accounts for the exogenous (observable) variables related to delayed childhood cancer care. Endogenous (unobservable) variables such as beliefs and attitudes were not included because of the lack of data. Further studies exploring these endogenous barriers to timely care are needed. Second, although our search strategy is optimally inclusive, we might have missed some studies, particularly grey literature from countries where national cancer programs are led by private organizations. Only three international organizations were searched by our team. Third, the heterogenous definition of childhood cancer across the literature is a persistent challenge. In this review, children were defined as persons up to 18 years old to be as inclusive as possible. Finally, we found considerable clinical heterogeneity to measure the timing of delays across the continuum of care, preventing us from performing a meta-analysis. While uniformity in definitions and criteria is ideal, challenges in performing clinical research in LMIC settings often means that studies must be adapted around local resources, customs, regulations, and data availability. Despite these limitations, this study is the most comprehensive review of predictors of delayed care among children living with cancer in LMICs.

5 | CONCLUSIONS

In LMICs, children with cancer face multifactorial barriers to access timely care across the entire continuum of care. We reviewed the current evidence of the key drivers of delays in care and found geographic, social, financial, health system, and health policy barriers that limit access to cancer care in LMICs. Based on these findings, we proposed a Three-Delay framework that can be used as a policy decision tool to guide financing streams and interventions to improve timely care and survival rates for children with cancer in LMICs. We encourage national governments and other public health leaders to use this tool as a template to explore their unique barriers and limitations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We want to thank Kenneth Carriveau from Moody Memorial Library (Baylor University) for contributing to the development of the systematic review portion of this study. We also want to thank Dr. Liang Wang from the Department of Public Health (Baylor University) for his support and contributions to the study design and early development.

DATA AVAILABILITY STATEMENT

The review protocol is publicly available on PROSPERO and Open Science Framework. All data used in the systematic review are available in the Supporting Information Appendix.

Abbreviations:

AACODS	Authority, Accuracy, Coverage, Objectivity, Date, Significance
CASP	Critical Appraisal Skills Program
GICC	Global Initiative for Childhood Cancer
HIC	high-income country
LMIC	low- and middle-income country
NIH	National Institutes of Health
PICO	Patient, Intervention, Comparison, Outcome
WHO	World Health Organization

REFERENCES

1. Force LM, Abdollahpour I, Advani SM, et al. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. Lancet Oncol. 2019;20(9):1211–1225. [PubMed: 31371206]
2. Joko-Fru WY, Parkin DM, Borok M, et al. Survival from childhood cancers in Eastern Africa: a population-based registry study. Int J Cancer. 2018;143(10):2409–2415. [PubMed: 29981149]
3. Knaul FM, Frenk J, Shulman L. Closing the Cancer Divide: A Blueprint to Expand Access in Low- and Middle-Income Countries. A Report of the Global Task Force on Expanded Access to Cancer Care and Control. Harvard Global Equity Initiative; 2011.
4. Rodriguez-Galindo C, Friedrich P, Morrissey L, Frazier L. Global challenges in pediatric oncology. Curr Opin Pediatr. 2013;25(1):3–15. [PubMed: 23295716]
5. Lam CG, Howard SC, Bouffet E, Pritchard-JonesK, Science and health for all children with cancer. Science. 2019;363(6432):1182. [PubMed: 30872518]
6. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014;15(1):35–47. [PubMed: 24314616]
7. Noone AM, Howlader N, Krapcho M, et al. SEER cancer statistics review 1975–2015. SEER; 2018; Accessed April 27, 2021. https://seer.cancer.gov/csr/1975_2015/
8. Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol. 2019;20(1):e42–e53. [PubMed: 30614477]

9. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol. 2017;18(6):719–731. [PubMed: 28410997]
10. Valsecchi MG, Steliarova-Foucher E. Cancer registration in developing countries: luxury or necessity? Lancet Oncol. 2008;9(2):159–167. [PubMed: 18237850]
11. Global Initiative for Childhood Cancer. World Health Organization; 2021. Accessed January 27, 2021. https://www.who.int/cancer/childhood-cancer/en/
12. Atun R, Bhakta N, Denburg A, et al. Sustainable care for children with cancer: a Lancet Oncology Commission. Lancet Oncol. 2020;21(4):e185–e224. [PubMed: 32240612]
13. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am. 2015;62(1):11–25. [PubMed: 25435109]
14. Wang YF, Wu LQ, Liu YN, Bi YY, Wang H. Gestational age and childhood leukemia: a meta-analysis of epidemiologic studies. Hematology. 2018;23(5):253–262. [PubMed: 29099685]
15. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. Neuro Oncol. 2019;21(11):1357–1375. [PubMed: 31301133]
16. Childhood cancer. World Health Organization; 2020. Accessed February 14, 2020. https://www.who.int/news-room/fact-sheets/detail/cancer-in-children
17. Berhane A, Hailu T, Mulugeta A. Determinants of delayed diagnosis among pediatric cancer patients from Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia. BMC Pediatr. 2019;19(1):478–485. [PubMed: 31810453]
18. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. Semin Pediatr Surg. 2012;21(2):136–141. [PubMed: 22475119]
19. Weaver MS, Yao AJ, Renner LA, Harif M, Lam CG. The prioritisation of paediatrics and palliative care in cancer control plans in Africa. Br J Cancer. 2015;112(12):1845–1856. [PubMed: 26042935]
20. Meara JGD, Leather AJMMS, Hagander LP, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet North Am Ed. 2015;386(9993):569–624.
21. Concepcion TL, Dahir S, Mohamed M, et al. Barriers to surgical care among children in Somaliland: an application of the three delays framework. World J Surg. 2020;44(6):1712–1718. [PubMed: 32030443]
22. Thaddeus S, Maine D. Too far to walk: maternal mortality in context. Soc Sci Med. 1994;38(8):1091–1110. [PubMed: 8042057]
23. Calvello EJ, Skog AP, Tenner AG, Wallis LA. Applying the lessons of maternal mortality reduction to global emergency health. Bull World Health Organ. 2015;93(6):417–423. [PubMed: 26240463]
24. Weed DL. The need for systematic reviews in oncology. J Natl Cancer Inst. 2018;110(8):812–814. [PubMed: 29618037]
25. Ndlovu S, Hlongwa M, Ginindza T. Mapping evidence on the risk factors associated with pediatric cancers in sub-Saharan Africa: a scoping review. Syst Rev. 2022;11(1):58–72. [PubMed: 35379332]
26. Gupta S, Howard S, Hunger S. Treating childhood cancer in low- and middle-income countries. In: Gelband H, Jha P, Sankaranarayanan R, eds. Cancer: Disease Control Priorities. 3rd ed. The International Bank for Reconstruction and Development/The World Bank; 2015.
27. World Health Assembly resolution WHA A70/A/CONF./9. Cancer prevention and control in the context of an integrated approach. World Health Organization. Accessed May 25, 2017. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_ACONF9-en.pdf?ua=1
28. Glanz K, Rimer BK, Viswanath K. Health Behavior: Theory, Research, and Practice. Wiley; 2015.
29. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. [PubMed: 33782057]
30. Cotache-Condor C, Grimm A, Williamson J, et al. Factors contributing to delayed childhood cancer care in low- and middle-income countries: a systematic review protocol. Pediatr Blood Cancer. 2022:e29.

31. Cotache-Condor C, Grimm A, Williamson J, et al. Factors contributing to delayed childhood cancer care in low- and middle-income countries: a systematic review protocol. Pediatr Blood Cancer. 2022;69(5):e29646. [PubMed: 35253351]
32. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc. 2006;2006:359–363. [PubMed: 17238363]
33. World Bank. World Bank country and lending groups. World Bank; 2021. Accessed June 1, 2021. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
34. Main classification table from the ICCC-3 based on ICD-O-3. National Cancer Institute; 2022. Accessed June 8, 2022. https://seer.cancer.gov/iccc/iccc3.html
35. EPPI-Reviewer 4.0: software for research synthesis [computer program]. EPPI; 2010.
36. Study quality assessment tools. National Institutes of Health; 2021. Accessed June 11, 2021. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
37. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res. 2020;7(1):7–17. [PubMed: 32111253]
38. CASP qualitative studies checklist. Critical Appraisal Skills Programme; 2019. Accessed May 19, 2021. https://casp-uk.net/casp-tools-checklists/
39. Tyndall J AACODS checklist. AACODS; 2010. Accessed May 19, 2021. https://dspace.flinders.edu.au/xmlui/bitstream/handle/2328/3326/AACODS_Checklist.pdf?sequence=4&isAllowed=y
40. Brown BJ, Adeleye AO, Ibeh JN. A prospective study on the causes of delayed diagnosis of childhood cancer in Ibadan, Nigeria. Pediatr Hematol Oncol J. 2015;32(6):365–373.
41. Walubita M, Bornwell S, Zulu JM. Challenges for health care providers, parents and patients who face a child hood cancer diagnosis in Zambia. BMC Health Serv Res. 2018;18(1):314–321. [PubMed: 29720168]
42. Fajardo-Gutiérrez A, Sandoval-Mex AM, Mejía-Aranguré JM, Rendón-Macías ME, Martínez-García Mdel C. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer. Med Pediatr Oncol. 2002;39(1):25–31. [PubMed: 12116075]
43. Ekenze SO, Nwangwu EI, Ezomike UO, Orji EI, Okafor OO. Continuing barriers to care of Wilms tumor in a low-income country. Pediatr Blood Cancer. 2019;66(1):e27416. [PubMed: 30152039]
44. Stefan DC, Siemonsma F. Delay and causes of delay in the diagnosis of childhood cancer in Africa. Pediatr Blood Cancer. 2011;56(1):80–85. [PubMed: 21108442]
45. Lins MM, Amorim M, Vilela P, et al. Delayed diagnosis of leukemia and association with morbid-mortality in children in Pernambuco, Brazil. J Pediatr Hematol Oncol. 2012;34(7):e271–e276. [PubMed: 22935656]
46. Abdelmabood S, Kandil S, Megahed A, Fouda A. Delays in diagnosis and treatment among children with cancer: Egyptian perspective. East Mediterr Health J. 2017;23(6):422–429. [PubMed: 28836655]
47. Handayani K, Sitaresmi MN, Supriyadi E, et al. Delays in diagnosis and treatment of childhood cancer in Indonesia. Pediatr Blood Cancer. 2016;63(12):2189–2196. [PubMed: 27510358]
48. Zahra Boutahar F, Benmiloud S, El Kababri M, et al. Time to diagnosis of pediatric brain tumors: a report from the Pediatric Hematology and Oncology Center in Rabat, Morocco. Childs Nerv Syst. 2018;34(12):2431–2440. [PubMed: 30054805]
49. Col Araz N, Guler E. Delays in diagnosis of childhood cancer in Southeastern Turkey and the associated factors. Pediatr Hematol Oncol. 2015;32(2):153–163. [PubMed: 24498898]
50. Berhane A, Hailu T, Mulugeta A. Determinants of delayed diagnosis among pediatric cancer patients from Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia. BMC Pediatr. 2019;19(1):478. [PubMed: 31810453]
51. Ramírez-Ortiz MA, Ponce-Castañeda MV, Cabrera-Muñoz ML, Medina-Sansón A, Liu X, Orjuela MA. Diagnostic delay and sociodemographic predictors of stage at diagnosis and mortality in unilateral and bilateral retinoblastoma. Cancer Epidemiol Biomarkers Prev. 2014;23(5):784–792. [PubMed: 24521997]

52. Chukwu BF, Ezenwosu OU, Ikefuna AN, Emodi IJ. Diagnostic delay in pediatric cancer in Enugu, Nigeria: a prospective study. Pediatr Hematol Oncol. 2015;32(2):164–171. [PubMed: 25251071]
53. Begum M, Islam MJ, Akhtar MW, Karim S. Evaluation of delays in diagnosis and treatment of childhood malignancies in Bangladesh. South Asian J Cancer. 2016;5(4):192–193. [PubMed: 28032088]
54. Abdelkhalek E, Sherief L, Kamal N, Soliman R. Factors associated with delayed cancer diagnosis in Egyptian children. Clin Med Insights Pediatr. 2014;8:39–44. [PubMed: 25232287]
55. Vasquez L, Oscanoa M, Tello M, Tapia E, Maza I, Geronimo J. Factors associated with the latency to diagnosis of childhood cancer in Peru. Pediatr Blood Cancer. 2016;63(11):1959–1965. [PubMed: 27394036]
56. Carpenter K, Slone AK, Scheuer M, Mehta PS, Slone JS. Factors influencing diagnostic delays of pediatric cancers in Botswana. Pediatr Blood Cancer. 2020;67(4):e28182. [PubMed: 31925921]
57. Buckle GC, Collins JP, Sumba PO, et al. Factors influencing time to diagnosis and initiation of treatment of endemic Burkitt lymphoma among children in Uganda and western Kenya: a cross-sectional survey. Infect Agent Cancer. 2013;8(1):36–51. [PubMed: 24079452]
58. Gilli IO, Joaquim AF, Tedeschi H, Dos Santos Aguiar S, Morcillo AM, Ghizoni E. Factors affecting diagnosis of primary pediatric central nervous system neoplasias in a developing country. Childs Nerv Syst. 2019;35(1):91–96. [PubMed: 30250987]
59. Brown BJ, Ajayi SO, Ogun OA, Oladokun RE. Factors influencing time to diagnosis of childhood cancer in Ibadan, Nigeria. Afr Health Sci. 2009;9(4):247–253. [PubMed: 21503176]
60. Grynszpancholc E, Pinto V, Ayoroa A, García L, Armesto A, Dran G. [Frequency and determinants of the delay in the diagnosis of cancer in children, in Argentina]. Medicina (B Aires). 2019;79(5):349–357. [PubMed: 31671384]
61. Chantada G, Fandiño A, Manzitti J, Urrutia L, Schvartzman E. Late diagnosis of retinoblastoma in a developing country. Arch Dis Child. 1999;80(2):171–174. [PubMed: 10325735]
62. Zapata-Tarrés M, González-Domínguez E, Doubova SV, et al. Patient and health service factors associated with delays in cancer treatment for children without social security in Mexico. Pediatr Blood Cancer. 2020;67(9):e28331. [PubMed: 32667140]
63. Essuman VA, Braimah IZ, Ndanu TA, Ntim-Amponsah CT. Presentation of children with advanced retinoblastoma for treatment in Ghana: the caretakers' perspectives. West Afr J Med. 2018;35(1):9–14. [PubMed: 29607471]
64. Fabian ID, Stacey AW, Foster A, et al. Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43 African countries and 518 patients from 40 European countries. Br J Ophthalmol. 2020;105(10):1435–1443. [PubMed: 32933936]
65. Masika GM, Gottvall M, Kohi WT, von Essen L, Dol JS. Concerns and needs of support among guardians of children on cancer treatment in Dar es Salaam: a qualitative study. Cancer Nurs. 2020;43(6):E342–E348. [PubMed: 31107702]
66. Leal-Cavazos C, Flores-Heredia M, Fernandez De Luna M, Vidal-Gutierrez O. Current factors related to advance stage retinoblastoma in a tertiary center in Mexico. Pediatr Blood Cancer. 2020;67(4):e28742. [PubMed: 33049088]
67. Mehrvar A, Faranoush M, Hedayati Asl AA, Tashvighi M, Mehrvar N, Gharehdaghi F. Delayed diagnosis, the critical landmark risk factor in management of retinoblastoma. Pediatr Blood Cancer. 2015;62(S4):S368.
68. Sherief L, Arafa S, Abdelkhalek E, Kamal N, Al Tehewi N. Delays in cancer diagnosis and treatment among children with cancer comparative study between Egyptian and Saudi centers. Pediatr Blood Cancer. 2015;62(S4):S217.
69. Zhang Y, Deng K, Zhu H, et al. Delays in diagnosis of pediatric histologically confirmed sellar germ cell tumors in China: a retrospective risk factor analysis. World Neurosurg. 2018;122:e472–e479. [PubMed: 30366141]
70. Tagoe L, Amegan-Aho K, Amoako E, Segbefia CI, Renner LA. Diagnostic delays in childhood cancer in a paediatric oncology unit in Ghana. Pediatr Blood Cancer. 2020;67(4):e28742. [PubMed: 33049088]
71. Oscanoa M Factors associated with time to diagnosis of childhood and adolescent non-Hodgkin lymphoma in Peru. Pediatr Blood Cancer. 2016;63:S182–S183.

72. Vasquez L, Oscanoa M, Tello M, Maza I, Paredes G, Geronimo J. Factors associated with time to diagnosis of childhood cancer: a retrospective cohort study. Pediatr Blood Cancer. 2015;62(S4):S217–S218.
73. Abdelkhalek ER, Sherif LM. Factors leading to delayed diagnosis of cancer in Egyptian children. Pediatr Blood Cancer. 2013;60:146. [PubMed: 22961710]
74. Kilicarslan-Toruner E, Akgun-Citak E. Information-seeking behaviours and decision-making process of parents of children with cancer. Eur J Oncol Nurs. 2013;17(2):176–183. [PubMed: 22521446]
75. Pulivadula Venkatasai J, Scott JX, Rajendran A, Manipriya R, Latha MS. Identification of issues involved in the road to diagnosis of childhood cancer in a developing country. Pediatr Blood Cancer. 2014;61:S399.
76. Pilkington M, Situma M, Winthrop A, Poenaru D. Quantifying delays and self-identified barriers to timely access to pediatric surgery at Mbarara Regional Referral Hospital, Uganda. J Pediatr Surg. 2018;53(5):1073–1079. [PubMed: 29548493]
77. De Angelis C, Pacheco C, Lucchini G, et al. The experience in Nicaragua: childhood leukemia in low income countries - the main cause of late diagnosis may be “medical delay.” Int J Pediatr. 2012;2012:1–5.
78. Papyan R The state of pediatric oncology in Armenia: challenges and achievements. Pediatr Blood Cancer. 2018;65:S195.
79. Cecen E, Gunes D, Mutafoglu K, Sarialioglu F, Olgun N. The time to diagnosis in childhood lymphomas and other solid tumors. Pediatr Blood Cancer. 2011;57(3):392–397. [PubMed: 21384539]
80. Afungchwi G, Hesseling P, Kimbi C, et al. Role of traditional medicine in burkitt lymphoma diagnosis and management in cameroon-necessity for collaboration. Pediatr Blood Cancer. 2015;62(S4):S160.
81. Gonzalez E, Zapata-Tarrés M, Arce D, et al. Socio-demographic characteristics and risk factors that influence the delay in the diagnosis of cancer in hospitals in Mexico. Pediatr Blood Cancer. 2018;65:S660–S661.
82. Ocak S, Sen HS, Turkkan E. The time to diagnosis and survival in children with solid tumors and lymphoma: results from a single center in Turkey. Pediatr Hematol Oncol. 2022;39(2):121–131. [PubMed: 34281453]
83. Bukha B, Dunn M, Mantzor S, Slone J. Delayed diagnosis of childhood cancers and health-seeking behaviors of caregivers in Botswana. Pediatr Blood Cancer. 2021;68(5):e29349. [PubMed: 34662504]
84. Nevarez L, Zapata M, Cardenas R, Velasco L. Analysis of healthcare system delay in pediatric patients with cancer attended at the national institute of pediatrics in Mexico. Pediatr Blood Cancer. 2020;67(4):e28742. [PubMed: 33049088]
85. Renner LA, McGill D. Exploring factors influencing health-seeking decisions and retention in childhood cancer treatment programmes: perspectives of parents in Ghana. Ghana Med J. 2016;50(3):149–156. [PubMed: 27752189]
86. Njuguna F, Martijn H, Langat S, et al. Factors influencing time to diagnosis and treatment among pediatric oncology patients in Kenya. Pediatr Hematol Oncol. 2016;33(3):186–199. [PubMed: 27184775]
87. Mulyowa I, Rose N. Assessing patient waiting time and associated factors on the Children’s Outpatient Department of Uganda Cancer Institute. Pediatr Blood Cancer. 2018;65:S558.
88. Schulze Schwering M, Gandiwa M, Msukwa G, Spitzer M, Kalua K, Molyneux EM. [Retinoblastoma in Malawi: why are admissions too late?]. Ophthalmologe. 2014;111(12):1189–1193. [PubMed: 25278348]
89. Offor UT, Akyea RK, Neequaye JE, Renner LA, Segbefia CI. The changing clinical pattern of endemic Burkitt lymphoma in Western Africa: experience from a tertiary center in Ghana. Pediatr Blood Cancer. 2018;65(10):e27275. [PubMed: 29873879]
90. Faruqui N, Joshi R, Martiniuk A, et al. A health care labyrinth: perspectives of caregivers on the journey to accessing timely cancer diagnosis and treatment for children in India. BMC Public Health. 2019;19(1):1613–1625. [PubMed: 31791308]

91. Pourfeizi A, Hosseini R, Sheervalilou R, Mehranfar S. Delays in initial referral, diagnosis, and treatment in children with cancer. Istanbul Tıp˙ Fakültesi Dergisi. 2020;83(3):259–266.
92. Balmant NV, de Paula Silva N, de O Santos M, de S Reis R, de Camargo B. Delays in the health care system for children, adolescents, and young adults with bone tumors in Brazil. J Pediatr (Rio J). 2018;95(6):744–751. [PubMed: 30075119]
93. Junquiera V Early diagnosis: the influence of training of primary health care professionals for suspicion of pediatric cancer in Brazil. Pediatr Blood Cancer. 2014;61:S121.
94. Baskin J, Qaddoumi I, Ahchu MS, et al. Evaluation of available resources for optimal care of children with brain tumors in central america. Neuro Oncol. 2011;13(3):iii98.
95. Ashraf T, Ahmed S, Tanveer S. Factors associated with delay in cancer diagnosis and treatment in children, a study from Northern Pakistan. Professional Med J. 2019;26(7):1156–1161.
96. Gavidia R, Fuentes SL, Vasquez R, et al. Low socioeconomic status is associated with prolonged times to assessment and treatment, sepsis and infectious death in pediatric fever in El Salvador. PLoS One. 2012;7(8):e43639. [PubMed: 22928008]
97. Osifo OD, Evbuomwan I, Efobi C. Management of childhood abdominal masses by Nigerian traditional doctors: a worrisome cause of delay in presentation. Pak J Med Sci. 2007;23(5):809–813.
98. Schroeder K, Alvi F, Johnston H, Masalu NA, Chao NJA. Impact of a pilot patient navigator program on pediatric cancer outcomes in a low resource setting. J Clin Oncol. 2019;37(15):e18152.
99. Hampejsková L, Bascaran C, Zondervan M. Gaps in essential retinoblastoma care in Africa. Pediatr Blood Cancer. 015;62(S4):S203.
100. Pondy Ongotsoyi AH, Molel Belika L, Coudja Ouabo Jerome C, et al. Pediatric palliative care in Cameroon: how to respond to the discontinuity of care? Med Palliat. 2019;18(4–5):195–199.
101. Adefehinti O, Adewara B, Badmus S. Prevalence, pattern and outcome of retinoblastoma in a tertiary centre in southwestern Nigeria: an 11-year review. Pediatr Blood Cancer. 2020;67(4):e28742. [PubMed: 33049088]
102. Resham S, Raza M, Muneeb A, et al. Prognostic factors for survival in paediatric patients with Ewing sarcoma in low-middle-income setting: a multicentre study. Pediatr Blood Cancer. 2018;65:S275.
103. Mills D, Abushanab S, Elhaloul A, El Nuweiry H, Shaaban MA, Salman Z. Unique barriers to care and outcomes of pediatric acute lymphoblastic leukemia treatment in Gaza city, occupied Palestinian territory. J Glob Oncol. 2017;3(2):25s–26s.
104. Lowe J, Arora R, Bagai P, Banerji U. Plotting healthcare journeys and exploring time taken for childhood cancer patients to access care in India. Pediatr Hematol Oncol J. 2018;3(3):S13.
105. Azad TD, Shrestha RK, Vaca S, et al. Pediatric central nervous system tumors in Nepal: retrospective analysis and literature review of low- and middle-income countries. World Neurosurg. 2015;84(6):1832–1837. [PubMed: 26283488]
106. Grynzspancholc E, Pinto V, Ayoroa A, Armesto A, García L, Dran G. Incidence and determinants of barriers to childhood cancer medication in a developing country. Pediatr Blood Cancer. 2018;65:S658.
107. Kashif R, Faizan M, Anwar S. Pediatric malignant mediastinal masses. J Coll Physicians Surg Pak. 2019;29(3):258–262. [PubMed: 30823954]
108. Asirwa FC, Njuguna F, Busakhala N. Burkitt lymphoma at a public pediatric referral cancer center in Western Kenya. Br J Haematol. 2015;171:88.
109. Salaverria C, Rossell N, Alabi SF, et al. Identifying causes of missing appointments and implementing interventions in real time increases treatment compliance and reduces abandonment rates for childhood cancer in El Salvador. Pediatr Blood Cancer. 2014;61:S252.
110. Rossell N, Salaverria C, Hernandez A, et al. Community resources support adherence to treatment for childhood cancer in El Salvador. J Psychosoc Oncol. 2018;36(3):319–332. [PubMed: 29452054]
111. Alvarez E, Seppa M, Rivas S, et al. Improvement in treatment abandonment in pediatric patients with cancer in Guatemala. Pediatr Blood Cancer. 2017;64(10):e26560.

112. Salaverria C, Rossell N, Hernandez A, et al. Interventions targeting absences increase adherence and reduce abandonment of childhood cancer treatment in El Salvador. Pediatr Blood Cancer. 2015;62(9):1609–1615. [PubMed: 25925227]
113. Ferman S, Lima F, Lage CRS, da Hora SS, Vianna DT, Thuler LC. Preventing treatment abandonment for children with solid tumors: a single-center experience in Brazil. Pediatr Blood Cancer. 2019;66(7):e27724. [PubMed: 30938082]
114. Kumar A, Roy Moulik N, Kulkarni K, Verma N. Prospective tracking of patients with acute lymphoblastic leukemia who abandoned therapy: parental perspectives, causes and implications of therapy abandonment from a tertiary cancer care centre. Pediatr Blood Cancer. 2014;61:S242.
115. Meremikwu MM, Ehiri JE, Nkanga DG, Udoh EE, Ikpatt OF, Alaje EO. Socioeconomic constraints to effective management of Burkitt's lymphoma in south-eastern Nigeria. Trop Med Int Health. 2005;10(1):92–98. [PubMed: 15655018]
116. Ishaya AI, Adah R. The role of socio-economic factors in abandonment of cancer treatment among paediatric patients in Jos Nigeria. Br J Med Med Res. 2016;13(4):1–7. 10.9734/BJMMR/2016/22283
117. Atwiine B, Busingye I, Kyarisiima R, et al. "Money was the problem": caregivers' self-reported reasons for abandoning their children's cancer treatment in southwest Uganda. Pediatr Blood Cancer. 2021;68(11):e29311. [PubMed: 34459106]
118. Borker AS, Chaudhary N. Pattern of refusal to treat and abandonment in a new pediatric oncology unit in southern india. Pediatr Blood Cancer. 2012;59(6):1100.
119. Slone JS, Chunda-Liyoka C, Perez M, et al. Pediatric malignancies, treatment outcomes and abandonment of pediatric cancer treatment in Zambia. PLoS One. 2014;9(2):e89102. [PubMed: 24586527]
120. Fadoo Z, Belgaumi A, Ashraf S, Imam U, Naqvi A, Nisar I. Reasons for early abandonment of treatment in children with acute lymphoblastic leukemia in a low middle income country. Pediatr Blood Cancer. 2013;60:71. [PubMed: 22434731]
121. Stanley CC, van der Gronde T, Westmoreland KD, et al. Risk factors and reasons for treatment abandonment among children with lymphoma in Malawi. Support Care Cancer. 2018;26(3):967–973. [PubMed: 28986643]
122. Libes J, Oruko O, Abdallah F, et al. Risk factors for abandonment of Wilms tumor therapy in Kenya. Pediatr Blood Cancer. 2015;62(2):252–256. [PubMed: 25382257]
123. Cai J, Yu J, Zhu X, et al. Treatment abandonment in childhood acute lymphoblastic leukaemia in China: a retrospective cohort study of the Chinese Children's Cancer Group. Arch Dis Child. 2019;104(6):522–529. [PubMed: 30705079]
124. Mostert S, Njuguna F, Langat SC, et al. Two overlooked contributors to abandonment of childhood cancer treatment in Kenya: parents' social network and experiences with hospital retention policies. Psychooncology. 2014;23(6):700–707. [PubMed: 24789661]
125. Ngoc Lan B, Castor A, Wiebe T, Toporski J, Moëll C, Hagander L. Adherence to childhood cancer treatment: a prospective cohort study from Northern Vietnam. BMJ Open. 2019;9(8):e026863.
126. Kumar A, Moulik NR, Mishra RK, Kumar D. Causes, outcome and prevention of abandonment in retinoblastoma in India. Pediatr Blood Cancer. 2013;60(5):771–775. [PubMed: 23303533]
127. Friedrich P, Lam CG, Kaur G, Itriago E, Ribeiro RC, Arora RS. Determinants of treatment abandonment in childhood cancer: results from a global survey. PLoS One. 2016;11(10):e0163090. [PubMed: 27736871]
128. Fluchel M, Hall L. Financial burden for caregivers of paediatric oncology patients in Kumasi, Ghana. Pediatr Blood Cancer. 2016;63:S279.
129. Mostert S, Njuguna F, van der Burgt RHM, et al. Health-care providers' perspectives on health-insurance access, waiving procedures, and hospital detention practices in Kenya. Pediatr Blood Cancer. 2018;65(8):e27221. [PubMed: 29741267]
130. Bonilla M, Rossell N, Salaverria C, et al. Prevalence and predictors of abandonment of therapy among children with cancer in El Salvador. Int J Cancer. 2009;125(9):2144–2146. [PubMed: 19585496]

131. Ehrlich BS, Movsisyan N, Batmunkh T, et al. Barriers to the early integration of palliative care in pediatric oncology in 11 Eurasian countries. Cancer. 2020;126(22):4984–4993. [PubMed: 32813913]

132. Ngwang J, Ngwa E. Burkitt lymphoma challenges in resource limited rural communities. Pediatr Blood Cancer. 2014;61:S320–S321.

133. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. Lancet Oncol. 2019;20(4):483–493. [PubMed: 30824204]

134. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087–m4098. [PubMed: 33148535]

135. Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. Lancet Oncol. 2008;9(8):721–729. [PubMed: 18672210]

136. Gupta S, Rivera-Luna R, Ribeiro RC, Howard SC. Pediatric oncology as the next global child health priority: the need for national childhood cancer strategies in low- and middle-income countries. PLoS Med. 2014;11(6):e1001656. [PubMed: 24936984]

137. Goss PE, Lee BL, Badovinac-Crnjevic T, et al. Planning cancer control in Latin America and the Caribbean. Lancet Oncol. 2013;14(5):391–436. [PubMed: 23628188]

138. Fleming KA, Horton S, Wilson ML, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet North Am Ed. 2021;398(10315):1997–2050.

139. Kruk ME, Gage AD, Arsenault C, et al. High-quality health systems in the sustainable development goals era: time for a revolution. Lancet Glob Health. 2018;6(11):e1196–e1252. [PubMed: 30196093]

140. CureAll framework: WHO Global Initiative for Childhood Cancer: increasing access, advancing quality, saving lives. World Health Organization; 2021.

141. European Network for Cancer research in Children and Adolescents. European Commission CORDIS; 2019. Accessed May 14, 2022. https://cordis.europa.eu/project/id/261474

142. Ribeiro RC, Antillon F, Pedrosa F, Pui CH. Global pediatric oncology: lessons from partnerships between high-income countries and low- to mid-income countries. J Clin Oncol. 2015;34(1):53–61. [PubMed: 26578620]

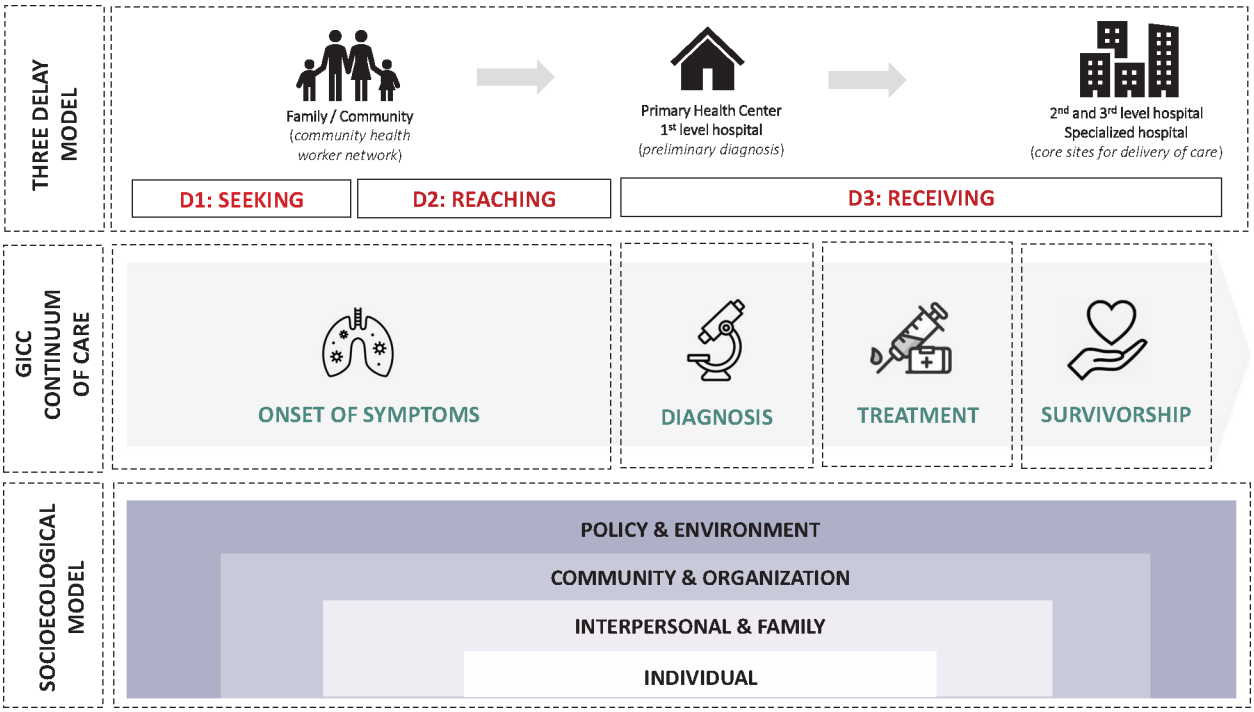

FIGURE 1.

Conceptual framework guiding the systematic review and adaptation of the final Three-Delay framework

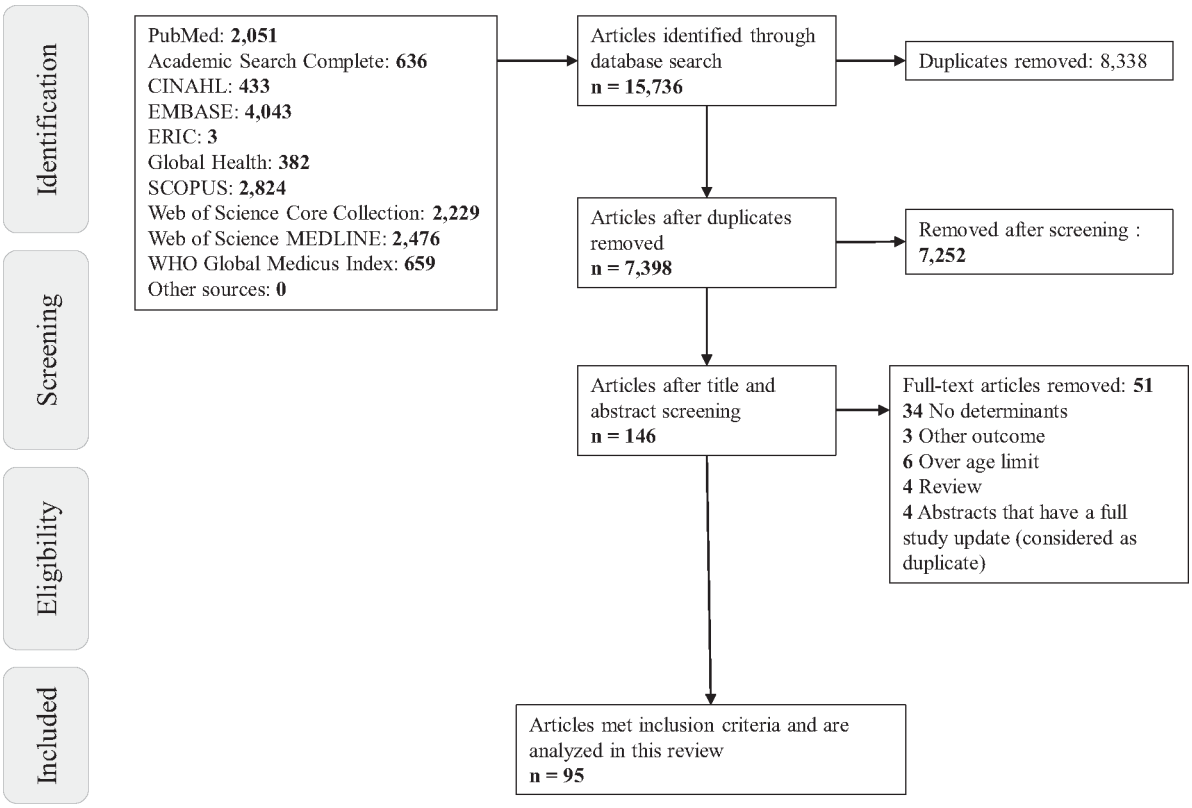

FIGURE 2.

Flowchart of systematic review. Note: Other sources include the World Bank Group, Institute for Health Metrics and Evaluation (IHME), theWHOInternational Agency for Research on Cancer (IARC)

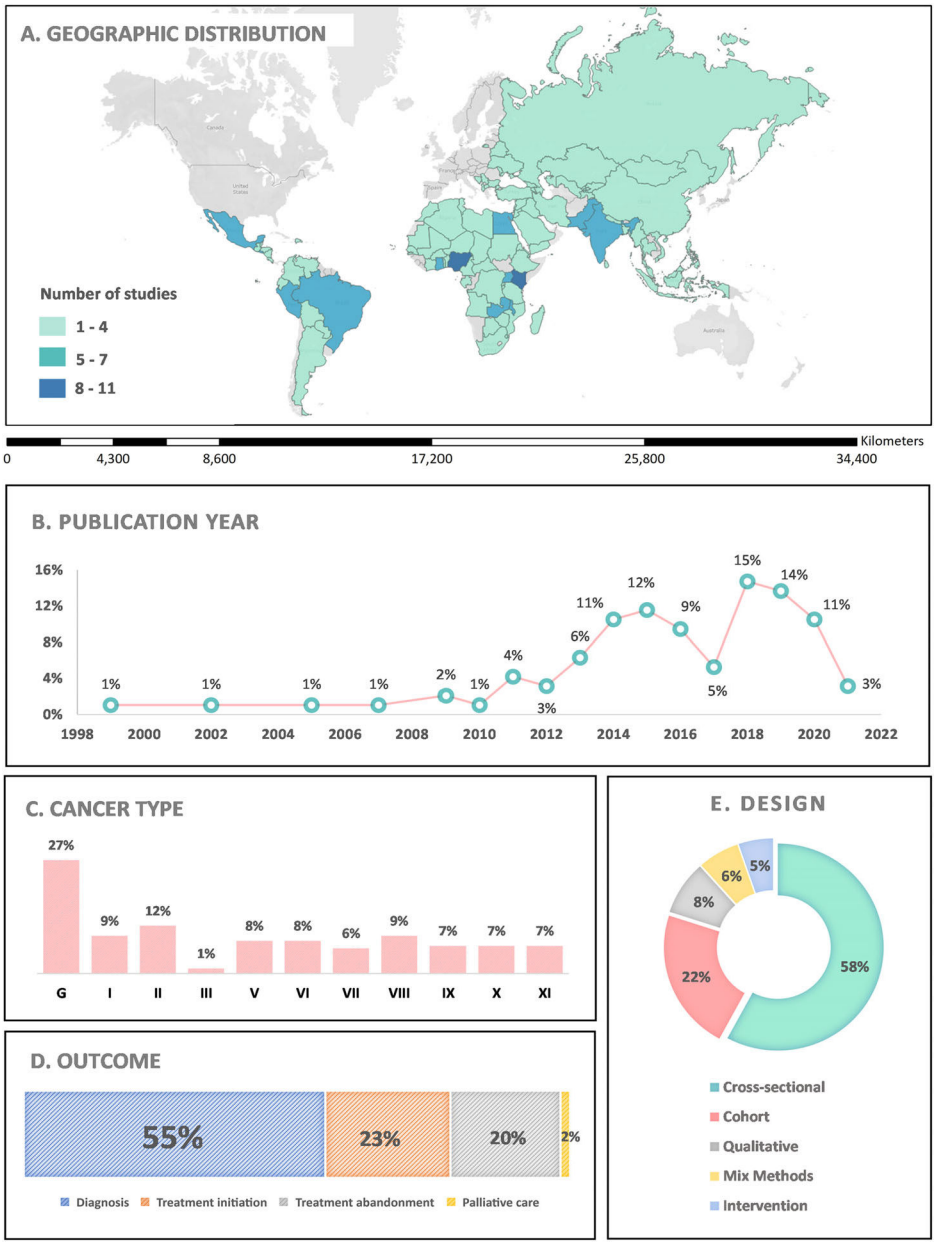

FIGURE 3.

Summary of descriptive statistics from 95 studies included in the systematic review by geographic location (A), publication year (B), childhood cancer type (C), outcomes (D), and study design (E). Note: Type of cancer was collapsed into 13 categories, including ICCC-3 categories (I = leukemias, myeloproliferative diseases, and myelodysplastic diseases; II = lymphomas and reticuloendothelial neoplasms; III = central nervous system and miscellaneous intracranial and intraspinal neoplasms; V = retinoblastoma; VI = renal tumors; VII = hepatic tumors; VIII = malignant bone tumors; IX = soft tissue and other extraosseous sarcomas; X = germ cell tumors, trophoblastic tumors, and neoplasms of gonads; XI = other malignant epithelial neoplasms and malignant melanomas) and one additional category for studies that addresses childhood cancers in general (G = general)

	ONSET OF SYMPTOMS		DIAGNOSTIC	REFERRAL	TREATMENT	PALLIATIVE CARE
INDIVIDUAL	Traditional medicine Religious beliefs Cancer beliefs Mistrust of health system Symptom presentation **Order of birth *** **Child age *** **Child sex ***	**Ethnic language ***	Lack of cancer knowledge (family) Traditional medicine Waiting time perception Solid tumors Extraocular retinoblastoma Tumors of central nervous system Attempt to save ocular globe Germinoma and slow growth for germ cell tumor		Lack of cancer knowledge (family) Sick caregiver Treatment toxicity Traditional medicine Not willing to enuclate Fear to side effects Perceived prognosis Race/ethnicity Religious beliefs Absence from work Symptom presentation **Waiting time perception *** **Cancer beliefs *** **Retinoblastoma diagnosis *** **Child sex *** **HIV status ***	
INTERPERSONAL & FAMILY	Parental age Number of children in household Household duties Source of income Lack of social support Absence from work **Parental education (both) *** **Paternal education *** **Maternal education *** **Dirt flooring *** **Large household size *** **Marital status ***	**Household income ***		**Household income ***	Lack of social support Farming occupation **Household income *** **Parental education (both) *** **Maternal education *** **Paternal education *** **Large household size ***	Family resistance Lack of social support
COMMUNITY & ORGANIZATION		Lack of transportation Lack of lodging **Travel distance *** **Rural population ***	Lack of cancer knowledge (health care personnel) Lack/inadequate infrastructure Misdiagnosis Multiple referrals **General physician *** **Type of clinic (public, private) *** **Primary level hospital ***	Lack of transportation **Having a central communication line *** **Rural population *** **Travel distance ***	Lack of transportation Lack of multidisciplinary care Poor communication systems between doctors and family Lack of pharmacy stock Unclear treatment plan Shortage of supplies Lack/inadequate infrastructure Hospital living conditions **Travel distance *** **Rural population ***	Lack of physician palliative care training Lack of home-based service
POLICY & ENVIRONMENT	**Country income level ***		Bureaucracy **No access to social security *** **Lack of health insurance *** **Country income level ***		Lack of education for children at hospital Hospital detention policy **Lack of health insurance ***	

FIGURE 4

Adaptation of the Three-Delay framework specific for childhood cancer care across the care continuum. Note: D1 = delay 1. D2 = delay 2. D3 = delay 3. The asterisk (*) and bold font indicates risk factors (RR, OR, HR, and aPR) of delayed childhood cancer as reported in the original studies. Determinants as risk factors in red font influence most domains in the framework

TABLE 1

Summary of characteristics of studies included in the systematic review investigating the association between risk factors of delayed childhood cancer care in low- and middle-income countries ($n = 95$)

Author	Design	Country	Setting	Determinant/factor	Outcome	Type of cancer
Brown[40]	CS	Nigeria	Hospital	Age	Diag.	General
Walubita[41]	Qual	Zambia	Hospital	Parents' or primary health workers' lack of knowledge; household poverty; inadequate counseling services; shortage of supplies (i.e., blood); inadequate infrastructure (i.e., beds); traditional medicine; religion	Diag.	General
Fajardo-Gutierrez[42]	CS	Mexico	Hospitals	Maternal education low; no social security; travel distance	Diag.	General
Ekenze[43]	CS	Nigeria	Hospital	Education; referral; traditional medicine	Diag.	Wilms tumor
Stefan[44]	CS	South Africa	Hospital	Physician delay	Diag.	General
Mendes Lins[45]	CS	Brazil	Hospital	Distance; public outpatient clinic; order of birth; parental age; number of children; parental education	Diag.	ALL AML
Abdelmabood[46]	CS	Egypt	Hospital	None	Diag.	General
Handayani[47]	CS	Indonesia	Hospital	Alternative medicine	Diag.	General
Zahra Boutahar[48]	CS	Morocco	Hospital	None	Diag.	Brain tumors
Col Araz[49]	CS	Turkey	Hospital	Physician delay; rural; first diagnosis by general physician; outpatient clinic	Diag.	Leukemia, lymphomas, solid tumors
Berhane[50]	CS	Ethiopia	Hospital	Age >10; rural; parental education; low income; health insurance; cancer beliefs; holy water	Diag.	General
Ramirez-Ortiz[51]	CS	Mexico	Hospital	Dirtflooring; maternal education	Diag.	Retinoblastoma
Chukwu[52]	Coh	Nigeria	Hospital	Patient delay; first center visited	Diag.	General
Begum[53]	CS	Bangladesh	Hospital	Age >2; father's low education; income	Diag.	General
Abdelkhalek[54]	CS	Egypt	2 Hospitals	Age; lower parental education; socioeconomic level	Diag.	General
Vasquez[55]	RC	Peru	Hospital	Older age; general physician	Diag.	Lymphoma, solid tumors
Carpenter[56]	RC	Botswana	Hospital	None	Diag.	General
Buckle[57]	CS	Uganda, Kenya	2 Hospitals	Financial; transportation; household duties; income; cancer perception; number of children; primary caretakers	Diag.	Burkitt lymphoma
Gilli[58]	CS	Brazil	Hospital	Urban residence; gait changes and paresis; father education level; gender; mother's occupation	Diag.	Central nervous system
Brown[59]	CS	Nigeria	Hospital	Health system delay	Diag.	General
Grynszpancholc[60]	CS	Argentina	ONG	Private clinics; primary level hospital	Diag.	General
Chantada[61]	CS	Argentina	Hospital	Elementary education	Diag.	Retinoblastoma

Author	Design	Country	Setting	Determinant/factor	Outcome	Type of cancer
Zapata-Tarres[62]	CS	Mexico	13 Hospitals	Lowest socioeconomic; highest socioeconomic; waiting time perception	Diag.	General
Essuman[63]	CS	Ghana	Hospital	Lack of awareness of cancer and financial barriers	Diag.	Retinoblastoma
Fabian[64]	CS	Multiple*	278 Health centers	Low-income level; lower middle-income level; age ≥22 months	Diag.	Retinoblastoma
Masika[65]	Qual	Tanzania	Hospital	Financial concerns; emotional concerns (parental guilt); need for information; need for tangible support; improvements in care practices; hospital living conditions; government assistance	Diag.	General
Leal-Cavazos[66]	CS	Mexico	n/d	Misdiagnosis; attempting globe salvage	Diag.	Retinoblastoma
Mehrvar[67]	CS	Iran	Hospital	Extraocular retinoblastoma	Diag.	Retinoblastoma
Sherief[68]	CS	Egypt	Hospital	Child age; parental age; education; socioeconomic status; maternal work; disease type	Diag.	General
Zhang[69]	RC	China	Hospital	Germinoma; slow growth	Diag.	Sellar germ cell tumors
Tagoe[70]	CS	Ghana	Hospital	Age; distance; malignancy type (solid tumor)	Diag.	Lymphomas, leukemia, retinoblastoma, Wilms tumor
Oscanoa[71]	RC	Peru	Hospital	None	Diag.	Non-Hodgkin lymphoma
Vasquez[72]	CS	Peru	n/d	Diagnosis by physician and not a pediatrician; advanced parental age; low level of education; older child	Diag.	Lymphoma, solid tumors
Abdelkhalek[73]	CS	Egypt	2 Hospitals	Low parental education; misdiagnosis; socioeconomic status	Diag.	General
Kilicarslan-Toruner[74]	Qual	Turkey	Hospital	Information sources; parental expectations of healthcare team; parental information needs/services; economic factors	Diag.	General
Pulivadula[75]	CS	India	n/d	Healthcare system delay; parental delay; rural; parental education; distance; diagnosis by general physician	Diag.	Hematological
Pilkington[76]	Qual	Uganda	Hospital	Home treatments; other responsibilities	Diag.	General
De Angelis[77]	CS	Nicaragua, Italy	2 Hospitals	Physician delay; patient delay; education/training programs on childhood oncological diseases	Diag.	ALL and AML
Papyan[78]	CS	Armenia	Hospital	Unavailability of registry; lack of essential services, multidisciplinary care, palliative support; costs	Diag.	Solid tumors, hematological
Cecen[79]	CS	Turkey	Hospital	Age; type of cancer/tumor; point of medical contact; metastasis at diagnosis	Diag.	Lymphoma, solid tumors
Afungchwi[80]	CS	Cameroon	3 Hospitals	Use of traditional medicine	Diag.	Burkitt lymphoma
Gonzalez[81]	CS	Mexico	15 Hospitals	Financial constraint; miss work; misdiagnosis	Diag.	Leukemia, lymphomas, solid tumors
Ocak[82]	CS	Turkey	Hospital	Age; paternal education; localization; tumor type	Diag.	Lymphoma, solid tumors
Bukha[83]	CS	Botswana	n/d	Brain tumors; age	Diag.	General
Nevarez[84]	CS	Mexico	Institute of pediatrics	Tumors of central nervous system	Diag., Treat. Init.	General

Author	Design	Country	Setting	Determinant/factor	Outcome	Type of cancer
Renner[85]	Qual	Ghana	Hospital	Parent's lack of knowledge; financial; traditional medicine; fear of Treat.; past experience in hospital	Diag., Treat. Init.	General
Njuguna[86]	CS	Kenya	Hospital	Healthcare delay; health insurance; alternative medicine; first center visited; hospital detention	Diag., Treat. Init.	General
Mulyowa[87]	CS	Uganda	Outpatient clinics	Poor adherence to treatment; missed appointment; failure or delay in initiation of necessary treatment	Diag., Treat. Init.	General
Schulze Schwering[88]	Qual	Malawi	Hospital	Parents' lack of knowledge; primary health workers' lack of knowledge of childhood cancers; referral was recommended with delay; traditional medicine; inadequate transport system; lack of free transport system	Diag., Treat. Init.	Retinoblastoma
Offor[89]	CS	Ghana	Hospital	Financial barriers	Diag., Treat. Init.	Burkitt lymphoma
Faruqui[90]	Qual	India	Hospital	Parents' or primary health workers' lack of knowledge; socioeconomic status; waiting times; lack of social support; multiple referrals; distance; unreliable public transport; traditional medicine; mistrust of health system; bureaucracy	Diag., Treat. Init.	General
Pourfeizi[91]	Mixed	Iran	Hospital	Perception of importance of primary symptoms; habitual delay in physician referral; low economic status; lack of family support; family problems; uncertainty about proposed treatment; high treatment costs	Diag., Treat. Init.	General
Balmant[92]	RC	Brazil	161 HOSPITALS	No past diagnosis; type of cancer; region of residence; age	Diag., Treat. Init.	Osteosarcoma, Ewing sarcoma
Junquiera[93]	Inter.	Brazil	Hospitals	Knowledge of childhood cancer among primary care providers; partnerships with specialized care services; existence of cancer care network	Diag., Treat. Init.	General
Baskin[94]	CS	Multiple*	Hospitals	Lacking adequate equipment; timely radiological tests; optimal radiation therapy; lack of multidisciplinary care	Diag., Treat. Init.	Brain tumors
Ashraf[95]	CS	Pakistan	Hospital	Age; type of malignancy; financial problems; distance; parental education status; perceptions about usefulness of treatment; use of alternative therapies	Diag., Treat. Init.	General
Gavidia[96]	PC	El Salvador	Hospital	Maternal illiteracy; anticipated travel time to hospital; low income; having a central line; belief about weather as a cause of illness	Diag., Treat. Init.	ALL and AML
Osifo[97]	RC	Nigeria	Hospital	Traditional medicine	Diag., Treat. Init.	General
Schroeder[98]	CS	Tanzania	Hospital	Treatment knowledge; complexity of care; limited provider capacity; poor care coordination	Diag., Treat. Init.	General
Hampejskova[99]	CS	Multiple*	Hospital	Healthcare professionals lack training	Diag., Treat. Init.	Retinoblastoma
Pondy[100]	CS	Cameroon	Hospital	Lack of financial means; use of other therapies	Diag., Treat. Init.	General
Adefehinti[101]	CS	Nigeria	Hospital	Financial constraint	Treat. Init.	Retinoblastoma
Resham[102]	CS	Pakistan	2 Hospitals	Insufficient resources; lack of access to medical care	Treat. Init.	Ewing sarcoma
Mills[103]	Coh	Gaza Strip	Hospital	Chemotherapy shortages; methotrexate monitoring; relapse; induction failure	Treat. Init.	ALL
Lowe[104]	Mixed	India	7 Hospitals	Contact with multiple physicians before diagnosis; distance	Treat. Init.	General

Author	Design	Country	Setting	Determinant/factor	Outcome	Type of cancer
Azad[105]	RC	Nepal	Hospital	Presenting symptoms; type of cancer	Treat. Init.	Central nervous system
Grynszpancholc[106]	CS	Argentina	Hospital	Lack of pharmacy stock; lack in the country/drug bank; unauthorized medicine	Treat. Init.	Leukemia, lymphomas, solid tumors
Kashif[107]	RC	Pakistan	Hospital	Education of father/guardian of the patient; primary diagnosis; medical professional delays	Treat. Init.	Malignant mediastinal
Asirwa[108]	CS	Kenya	2 Hospitals	HIV; early relapse; high cost of cancer treatment; lack of social support; long distances traveled to the hospital	Treat. Aban.	Burkitt lymphoma
Salaverria[109]	Inter.	El Salvador	Hospital	Cultural and social factors	Treat. Aban.	ALL
Rossell[110]	Mixed	El Salvador	Community centers	Lack or irregular access to institutional contact persons; lack of transportation; lack of financial resources	Treat. Aban.	General
Alvarez[111]	RC	Guatemala	Hospitals	Distance; age; time since diagnosis; race/ethnicity	Treat. Aban.	General
Salaverria[112]	Inter.	El Salvador	Hospital	Weather; transportation; financial instability; caregiver ill or unable to leave work; caregiver error (forgetting appointment date); palliative care as an alternative; fear of treatment effects	Treat. Aban.	General
Ferman[113]	Inter.	Brazil	Hospital	Retinoblastoma diagnosis	Treat. Aban.	Solid tumors
Kumar[114]	RC	India	Hospital	Illiteracy; financial constraints;false perceptions about cure	Treat. Aban.	ALL
Meremikwu[115]	RC	Nigeria	Hospital	Costs of testing; financial constraints	Treat. Aban.	Burkitt lymphoma
Ishaya[116]	RC	Nigeria	Hospital	Large household size; mother as caregiver; travel time to hospital >2 hours; age	Treat. Aban.	General
Atwiine[117]	Qual	Uganda	Household	Financial; competing commitments; child looked cured; alternative treatment; cancer is incurable; side effects	Treat. Aban.	General
Borker[118]	CS	India	Hospital	Socioeconomic constraints; religious beliefs; fatalistic attitude; alternative therapies	Treat. Aban.	Leukemia and solid tumors
Slone[119]	RC	Zambia	Hospital	Region of residence; maternal education less than secondary school; negative hiv status	Treat. Aban.	General
Fadoo[120]	PC	Pakistan	3 Hospitals	Age; residence; paternal education; maternal education; ethnicity and language	Treat. Aban.	ALL
Stanley[121]	Mixed	Malawi	Hospital	Lack of guardian education; travel times; community influence; costs; suboptimal clinical logistical challenges	Treat. Aban.	Lymphoma
Libes[122]	Inter.	Kenya	4 Hospitals	Financial; misunderstanding of treatment plan	Treat. Aban.	Wilms tumor
Cai[123]	CS	China	20 Hospitals	Low income; money; education; rural; farmer	Treat. Aban.	ALL
Mostert[124]	CS	Kenya	Hospital	Alternative medicine; cancer perception; forced hospital stays; financial; health insurance	Treat. Aban.	General
Ngoc[125]	PC	Vietnam	Hospital	Poor prognosis; travel distance; gender; poverty; traditional medicine	Treat. Aban.	General
Kumar[126]	PC	India	Hospital	Rural; financial; not willing to enucleate	Treat. Aban.	Retinoblastoma

Author	Design	Country	Setting	Determinant/factor	Outcome	Type of cancer
Friedrich[127]	Mixed	Multiple*	n/d	Socioeconomic status; education; travel time; treatment-related concerns; perceived prognosis; fear; awareness	Treat. Aban.	General
Fluchel[128]	CS	Ghana	Hospital	Financial burden for caregivers	Treat. Aban.	General
Mostert[129]	CS	Kenya	Hospital	Health insurance access; fee waiver procedures when payment is not made; hospital detention practices	Treat. Aban.	General
Bonilla[130]	RC	El Salvador	Hospital	Paternal illiteracy; maternal illiteracy; increasing number of household members; low monthly household income	Treat. Aban.	General
Ehrlich[131]	Mixed	Multiple*	n/d	Lack of physician palliative care training; lack of access to consultation; lack of home-based services; family resistance to palliative care; lack of healthcare workforce/resources	Palliative care	General
Ngwang[132]	CS	Cameroon	n/d	Cultural views and beliefs; lack of health units; inaccessibility of treatment products	Palliative care	Burkitt lymphoma

Abbreviations: Coh, cohort; CS, cross-sectional; Diag., diagnosis; Inter., intervention; Mixed, mixed methods; n/d, not detailed; PC, prospective cohort; QL, qualitative; RC, retrospective cohort; Treat. Aban., treatment abandonment; Treat. Init., treatment initiation.

Pediatr Blood Cancer. Author manuscript; available in PMC 2024 March 27.